Amendments to the Drawings:

The attached sheet of drawing includes changes to Fig. 11. This sheet replaces the original sheet of Figure 11.

Attachment: Replacement Sheet

REMARKS/ARGUMENTS

Reconsideration of the above-identified application is respectfully requested.

In the Office Action dated May 16, 2006, the drawings are objected to because Figure 11 is partially illegible.

The Office Action also noted that the color photographs are not accepted unless a petition filed under 37 CFR 1.84(a)(2) is granted, and that the trademarks in the specification should be capitalized.

Claims 1-29 are pending. Claims 1-14 are elected for further examination and are rejected.

Claims 7-9 and 10-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Claims 1-14 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Claims 1-12 and 14 are rejected under 35 U.S.C. § 102(b) as being anticipated by Zhong et al.

Claims 1-3 and 12-14 are rejected 35 U.S.C. § 102(a) as being anticipated by Her et al.

Claims 1, 6 and 10-12 are rejected under 35 U.S.C. § 102(b) as being anticipated by Falk et al.

Claims 1, 6 and 10-12 are rejected under 35 U.S.C. § 102(b) as being anticipated by Simon et al.

Claims 1, 12 and 14 are rejected under 35 U.S.C. § 102(a) as being anticipated by Gerard et al.

Claims 1, 6, 10 and 11-12 are rejected under 35 U.S.C. § 102(e) as being anticipated by Yamanouchi et al.

Claims 1, 12 and 14 are rejected under 35 U.S.C. § 102(e) as being anticipated by Hogaboam et al.

Claims 1, 4-6, 8-9, 12 and 14 are rejected under 35 U.S.C. § 102(a) as being anticipated by GenBank Accession Nos. AL929535 and AC139623.

Claims 1, 4-6 and 8-9 are rejected under 35 U.S.C. § 102(a) as being anticipated by GenBank Accession No. BX240588.

Applicants acknowledged the receipt of PTO-892 and PTO/SB/08.

In response to the objection, Applicants have submitted a set of replacement sheets including a replacement drawing of Fig. 11, and amended the specification to capitalize the trademarks and provide the generic terminology of the trademarks in parenthesis.

In response to the rejections, Applicants have amended claims 1, 4-12, and 14 to further clarify the claimed invention, and deleted claim 2. No new matter has been introduced.

Applicants respectfully submit that the amendments have overcome the rejections for the reasons set forth below:

Drawings

The drawings are objected to because Figure 11 is partially illegible. In response to this objection, a replacement sheet of Figure 11 is submitted. Applicants respectfully submit that the grounds for the objection have been obviated. Withdrawal of the

objection to the drawing is respectfully requested. Applicants will file a petition for color drawings upon allowance of the pending claims.

Specification

The Office Action noted that the trademarks in the specification should be capitalized and be accompanied by the generic terminology.

In response to the rejections, the trademarks have been amended and the corresponding generic terminology of the trademarks has been provided.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 7-9 and 10-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for reasons stated on pages 4-5 of the Office Action.

With respect to claim 7, the Office Action alleges that the meaning of the phrase "isolated from upstream region of zebrafish L-FABP" is not clear because L-FABP is a protein. Applicants have amended claim 7 to replace the phrase "upstream region of zebrafish L-FABP" with the phrase "upstream region of a gene encoding a zebrafish L-FABP gene."

With respect to claims 8, 10 and 11, the Office Action alleges that there is insufficient antecedent basis for the limitation "said nucleic acid sequence of SEQ ID NO:1."

In respond to the rejections, Applicants have amended the claims to depend upon claim 6 instead of claim 1, which provides antecedent basis for "said nucleic acid sequence of SEQ ID NO:1."

With respect to claim 12 and 14, the Office Action alleges that the metes and bounds of the phrase "basal promoter" are not clear. In order to expedite prosecution, Applicants have amended claims 12 and 14 to replace the phrase "basal promoter" with the phrase "core promoter." The amendment is supported by the specification at least on page 22, lines 25 to page 23, line 2. The meaning of "core promoter" is well-defined in the art. For example, Wikipedia, the free on-line encyclopedia defines core promoter as an element containing the transcription start site (TSS), the sequence from -1 to -35 from the TSS, and a binding site for RNA polymerase (see Exhibit 1).

Applicants respectfully submit that the amendments obviate the grounds of the rejection. Withdrawal of the rejection to claims 7-9 and 10-14 under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-14 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement for reasons stated on pages 5-8 of the Office Action. Specifically, the Office Action alleges that Applicants fail to provide adequate written description for "an isolated polynucleotide comprising a liver-specific expression control sequence that modulates expression of vertebrate liver fatty acid binding protein (L-FABP)." The Office Action also alleges that Applicants fail to provide an indication of how the sequences of SEQ ID NOS:1-3 are representative of variants having at least 80% homology to these sequences.

In response to the rejection, Applicants have amended claim 1 to recite "an isolated polynucleotide comprising a liver-specific expression control sequence from a

fish that modulates expression of a vertebrate liver fatty acid binding protein (L-FABP)." The amended phrase is fully supported in the specification by SEQ ID NOS:1-3.

Applicants have also amended claims 6, 8, 10 and 11 to recite "a functional variant." The specification has provided detailed descriptions for "functional variants" on page 10, lines 14-17 and on page 12, lines 4-14.

Applicants respectfully submit that the amendments obviate the grounds for the rejection. Withdrawal of the rejection to claims 1-14 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejections Under 35 U.S.C. § 102

Claims 1-12 and 14 are rejected under 35 U.S.C. § 102(b) over Zhong et al. for reasons stated on pages 9-10 of the Office Action. Specifically, the Office Action alleges that that Zhong inherently contain a liver-specific expression control sequence.

For anticipation under 35 U.S.C. §102, the reference "must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present." (MPEP §706.02, IV. Distinction between 35 U.S.C. 102 and 103, page 700-21). The Federal Circuit has held that prior art is anticipatory only if every element of the claimed invention is disclosed in a single item of prior art in the form literally defined in the claim. *See e.g., Jamesbury Corp. v. Litton Indus. Products*, 756 F.2d 1556, (Fed. Cir. 1985); *See also Atlas Powder Co. v. DuPont;* 750 F.2d 1569, (Fed. Cir. 1984); *American Hospital Suppl v. Travenol Labs*, 745 F.2d 1 (Fed. Cir. 1984).

Zhong describes the construction of a zebrafish genomic library from zebrafish embryos in yeast artificial chromosomes. Zhong does not disclose "an isolated

polynucleotide comprising a liver-specific expression control sequence from a fish that modulates expression of a vertebrate liver fatty acid binding protein (L-FABP)," as recited in claim 1.

The Office Action alleges that Zhong would inherently contain "a basal promoter of a zebrafish isolated polynucleotide comprising a liver-specific expression control sequence from upstream of a gene for L-FABP" Applicants respectfully disagree.

Although Zhong's library provides coverage of the zebrafish genome in about 17,000 clones with an average insert size of 470 kb, there is no guarantee that among these clones, "the liver-specific expression control sequence from a fish that modulates expression of a vertebrate liver fatty acid binding protein (L-FABP)" are included. It should be noted that the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of the result or characteristic. *In re Rijckert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993). Inherency may not be established by probabilities or possibilities. The missing limitation must be necessarily present in the thing described in the reference (see e.g., MPEP 2112 IV). Accordingly, the mere possibility that Zhong may have a clone containing the claimed sequence is not enough for a 102 rejection based on inherency.

Moreover, even if Zhong's library contains a clone having the claimed sequence, it is well established that a disclosed generic formula anticipates a specific species covered by the formula only if the species can be "at once envisaged" from the formula (*see e.g.*, MPEP 2131.02). In the instant case, Zhong simply discloses the generation of a genomic library for zebrafish. The reference does not provide the sequences of all clones, nor does it provide any guidance as to which clones contain the claimed sequence,

and where the claimed sequence might be located in these clones. Accordingly, the claimed sequence cannot be "at once envisaged" from the teachings of Zhong.

Accordingly, Applicants respectfully submit that Zhong fails to teach a "an isolated polynucleotide comprising a liver-specific expression control sequence from a fish that modulates expression of a vertebrate liver fatty acid binding protein (L-FABP)," as recited in claim 1. Therefore, claim 1 is not anticipated by Zhong. Claims 2-14 are also patentable over Zhong because they depend from claim 1 and recite additional patentable subject matter. Withdrawal of the rejection to claims 1-14 under 35 U.S.C. § 102(b) over Zhong is respectfully requested.

Claims 1-3 and 12-14 are rejected under 35 U.S.C. § 102(a) over Her et al. for reasons stated on pages 10-11 of the Office Action. Applicants respectfully submit that Her et al. describes inventors' own invention and was published less than a year before the priority date of the instant application. The two middle authors of Her et al., Chia-Chang Chiang and Wen-Ya Chen, did not contribute to the conception of the claimed invention. Applicants have enclosed a Declaration of Dr. Jen-Leih Wu under 37 CFR 1.132 to state this fact. (see Exhibit 2). Accordingly, Her does not constitute a prior art under 35 U.S.C. § 102(a). Withdrawal of the rejection to claims 1-3 and 12-14 under 35 U.S.C. § 102(a) over Her is respectfully requested.

Claims 1, 6 and 10-12 are rejected under 35 U.S.C. § 102(b) over Falk et al. Claims 1, 6 and 10-12 are rejected under 35 U.S.C. § 102(b) over by Simon et al. Claims 1, 12 and 14 are rejected under 35 U.S.C. § 102(a) as being anticipated by Gerard et al. Claims 1, 6, 10 and 11-12 are rejected under 35 U.S.C. § 102(e) over Yamanouchi et al. Claims 1, 12 and 14 are rejected under 35 U.S.C. § 102(e) over Hogaboam et al. Claims

1, 4-6, 8-9, 12 and 14 are rejected under 35 U.S.C. § 102(a) over GenBank Accession Nos. AL929535 and AC139623. Claims 1, 4-6 and 8-9 are rejected under 35 U.S.C. § 102(a) over GenBank Accession No. BX240588.

Claim 1, as amended, recites "an isolated polynucleotide comprising a liver-specific expression control sequence from a fish that modulates expression of a vertebrate liver fatty acid binding protein (L-FABP)." Falk describes a rat Fabp-I promoter (nt 1-617) linked to a transgene. Simon describes various cis-acting elements of rat Fabpl gene linked to a hGH reporter gene. Gerard describes liver-specific expression of ApoA-1 using liver specific promoters such as α1-antitrypsin, apoA-1, liver fatty acid binding protein, LDL receptor, or plasminogen activator inhibitor type 1 gene promoter. Yamanouchi describes isolation of 5' upstream sequence of human L-FABP gene. Hogaboam describes liver-specific expression of CXC chemokines using liver specific promoters such as α1-antitrypsin, apoA-1, liver fatty acid binding protein, LDL receptor, or plasminogen activator inhibitor type 1 gene promoter. None of these references disclose a liver-specific expression control sequence from a fish. Accordingly, claim 1, as amended, is not anticipated by Falk, Simon, Gerard, Yamanouchi or Hogaboam. Claims 6, 10-12 and 14 are patentable over Falk, Simon, Gerard, Yamanouchi or Hogaboam because they depend from claim 1.

GenBank Accession No. AL929535 is a 162435 base pair zebrafish DNA sequence. GenBank Accession No. AC139623 is a 203371 bp zebrafish DNA sequence. GenBank Accession No. BX240588 is a 738 bp zebrafish DNA sequence. These sequences do not specifically disclose "an isolated polynucleotide comprising a liver-specific expression control sequence from a fish that modulates expression of a vertebrate

liver fatty acid binding protein (L-FABP)," as recited in claim 1, nor do they provide any guidance on how to locate such a sequence. The Office Action noted that the sequences contain regions sharing high homology with SEQ ID NOS:4-9. However, the existence of SEQ ID NOS:4-9 simply suggests that the cited sequences **may** contain a liver-specific expression control sequence that modulates expression of a vertebrate liver fatty acid binding protein (L-FABP). As discussed above, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of the result or characteristic. *In re Rijckert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993). Accordingly, claim 1 is not anticipated by GenBank Accession Nos. AL929535, AC139623, and BX240588. Claims 4-6, 8-9, 12 and 14 are patentable over GenBank Accession Nos. AL929535, AC139623, and BX240588 because they depend from claim 1.

Moreover, all rejections to claims 6, 10, and 11 are based on the interpretation that "a nucleic acid sequence of..." encompasses any two or more contiguous nucleotides of the claimed sequence. Claims 6, 10, and 11 have been amended to recite "the a nucleic acid sequence of...."

Taken together, Applicants respectfully submit that the grounds for the rejections under 35 USC §102 have been obviated. Withdrawal of the rejections is respectfully requested.

In view of the foregoing remarks, favorable reconsideration of all pending claims is requested. Applicants respectfully submit that this application is in condition for allowance and request that a notice of allowance be issued. Should the Examiner believe that anything further is required to expedite the prosecution of this application or further clarify the issues, the Examiner is requested to contact Applicants' attorney at the telephone number listed below.

Respectfully submitted,

Dated: **August 15, 2006**

Fei-Fei Chao
Registration No. 43,538
Andrews Kurth LLP
1350 I Street, NW
Suite 1100
Washington, D.C. 20005
Telephone: (202) 662-3036
Fax: (202) 662-2739

Enclosures: Exhibit 1: Copy of the definition for "core promoter" from Wikipedia
Exhibit 2: Declaration under 37 C.F.R. §1.132 from Jen-Leih Wu

Promoter

From Wikipedia, the free encyclopedia

In genetics, a **promoter** is a DNA sequence that enables a gene to be transcribed. The promoter is recognized by RNA polymerase, which then initiates transcription. In RNA synthesis, promoters are a means to demarcate which genes should be used for messenger RNA creation - and, by extension, control which proteins the cell manufactures.

The perfect promoter is called a canonical sequence.

Contents

Promoter elements

- Core promoter
  - Transcription Start Site (TSS)
  - Approximately -35
  - A binding site for RNA polymerase
    - RNA polymerase I: transcribes genes encoding ribosomal RNA
    - RNA polymerase II: transcribes genes encoding messenger RNA and certain small nuclear RNAs
    - RNA polymerase III: transcribes genes encoding tRNAs and other small RNAs
  - General transcription factor binding sites
- Proximal promoter
  - Approximately -250
  - Specific transcription factor binding sites
- Distal promoter
  - Anything further upstream (but not an enhancer or other regulatory region whose influence is positional/orientation independent)
  - Specific transcription factor binding sites

Promoters represent critical elements that can work in concert with other regulatory regions (enhancers, silencer (DNA), boundary elements/insulators) to direct the level of transcription of a given gene.

The usage of canonical sequence for a promoter is problematic, and should be clarified. Canonical implies perfect, in some sense. In the case of a transcription factor binding site, then there may be a single sequence which binds the protein most strongly under specified cellular conditions. This might be called canonical. However, natural selection may favor less energetic binding as a way of regulating transcriptional output. In this case, we may call the most common sequence in a population, the wild-type sequence. It may not even be the most advantageous sequence to have under prevailing conditions. Recent evidence also indicates that several genes (including the proto-oncogene c-myc) have G-quadruplex motifs as potential regulatory signals.

A major question in evolutionary biology is how important tinkering with promoter sequences is to evolutionary change, for example, the changes that have occurred in the human lineage after separating from chimps. Some evolutionary biologists, for example Allan Wilson, have proposed that evolution in promoter or regulatory regions may be more important than changes in coding sequences over such time frames.

Promoter sequences

Prokaryotic promoters

In prokaryotes, the promoter consists of two short sequences at -10 and -35 position *upstream* of the gene, that is, prior to the gene in the direction of transcription. The sequence at -10 is called the Pribnow box and usually consists of the six nucleotides TATAAT. The Pribnow box is absolutely essential to start transcription in prokaryotes. The other sequence at -35 usually consists of the six nucleotides TTGACA. Its presence allows a very high transcription rate.

```
   <-- upstream                                                                    downstream -->
5'-XXXXXXXPPPPPXXXXXXPPPPPPXXXXGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGXXXX-3'
           -35       -10       Gene to be transcribed
.
(note that the optimal spacing between the -35 and -10 sequences is 19 nt)
```

Probability of occurrence of each nucleotide

```
 for -10 sequence
 T    A    T    A    A    T
77%  76%  60%  61%  56%  82%
```

```
 for -35 sequence
 T    T    G    A    C    A
69%  79%  61%  56%  54%  54%
```

Eukaryotic promoters

Eukaryotic promoters are extremely diverse and are difficult to characterize. They typically lie upstream of the gene and can have regulatory elements several kilobases away from the transcriptional start site. In eukaryotes, the transcriptional complex can cause the DNA to bend back on itself, which allows for placement of regulatory sequences far from the actual site of transcription. Many eukaryotic promoters, but by no means all, contain a TATA box (sequence TATAAA), which in turn binds a TATA binding protein which assists in the formation of the RNA polymerase transcriptional complex. The TATA box typically lies very close to the transcriptional start site (often within 50 bases).

Eukaryotic promoter regulatory sequences typically bind proteins called transcription factors which are involved in the formation of the transcriptional complex. An example is the E-box (sequence CACGTG), which binds transcription factors in the basic-helix-loop-helix (bHLH) family (e.g. BMAL1-Clock, cMyc).

See Michael Levine and Robert Tjian. "Transcription regulation and animal diversity". *Nature* 424, 147 - 151 (10

July 2003) [1] (http://bioweb.usc.edu/courses/2003-fall/documents/bisc320-gp_article1.pdf)

Binding

The binding of a promoter sequence (P) to a sigma factor-RNAP complex (R) is a two-step process:

1. R+P ↔ RP(closed). K = 10E7
2. RP(closed) --> RP(open). K = 10E−2

Diseases associated with aberrant promoter function

Though OMIM is a major resource for gathering information on the relationship between mutations and natural variation in gene sequence and susceptibility to hundreds of diseases, it requires a sophisticated search strategy to extract those diseases that are associated with defects in transcriptional control where the promoter is believed to have direct involvement. This is a list of diseases that evidence suggests have some involvement of promoter malfunction, either through direct mutation of a promoter sequence or mutation in a transcription factor or transcriptional co-activator. Keep in mind that most diseases are heterogeneous in etiology, meaning that one "disease" is often many different diseases at the molecular level, though the symptoms exhibited and the response to treatment might be identical. How diseases respond differently to treatment as a result of differences in the underlying molecular origins is partially addressed by the discipline of pharmacogenomics. Not listed here are the many kinds of cancers that involve aberrant changes in transcriptional regulation owing to the creation of chimeric genes through pathological chromosomal translocation.

- Asthma
  - population genetics study: Hobbs, K.; Negri, J.; Klinnert, M.; Rosenwasser, L.J.; and Borish, L. (1998). Interleukin-10 and transforming growth factor-beta promoter polymorphisms in allergies and asthma (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9847292). *Am J Respir Crit Care Med.* **158** (6), 1958-1962.
  - population genetics study: Burchard, E.G.; Silverman, E.K.; Rosenwasser, L.J.; Borish, L.; Yandava, C.; Pillari, A.; Weiss, S.T.; Hasday, J.; Lilly, C.M.; Ford, J.G.; and Drazen, J.M. (1999). Association between a sequence variant in the IL-4 gene promoter and FEV(1) in asthma (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10471619). *Am J Respir Crit Care Med.* **160** (3), 919-922.

- Beta thalassemia
  - case study: Kulozik, A.E.; Bellan-Koch, A.; Bail, S.; Kohne, E.; and Kleihauer, E. (1991). Thalassemia intermedia: moderate reduction of beta globin gene transcriptional activity by a novel mutation of the proximal CACCC promoter element (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2018842). *Blood.* **77** (9), 2054-2058.

- Rubinstein-Taybi syndrome
  - case study: Petrij F, Giles RH, Dauwerse HG, Saris JJ, Hennekam RC, Masuno M, Tommerup N, van Ommen GJ, Goodman RH, Peters DJ, et al. (1995). Rubinstein-Taybi syndrome caused by mutations in the transcriptional co-activator CBP (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7630403). *Nature.* **376** (6538), 348-351.

Category: Gene expression